REMARKS

The present application is directed to a method of causing expression of a desired heterologous protein in mucosal cells by placing a nucleotide sequence encoding the protein to be expressed under the control of a promoter in a recombinant gut-colonizing bacterium, orally administering the bacterium to a mammal, and causing expression of the protein. The application also includes a method of inducing a serum or mucosal antibody response against *Yersinia pestis*. The recombinant bacteria are useful for protecting humans against potential biological warfare agents such as plague.

Following entry of this amendment Claims 1, 23, 26-31 and 33-35 will be pending. Claims 1, 23, 26 and 31 are amended. Claims 2-22, 24-25 and 32 are cancelled without prejudice, and Claims 33-35 are new. No new matter is added and support for the amendments can be found throughout the specification.

Claim rejections under 35 U.S.C. § 112, first paragraph

In the Office Action mailed May 2, 2007, the Examiner rejected Claim 1 and those claims dependent therefrom under 35 U.S.C. § 112, first paragraph, as containing new matter. Applicants respectfully submit that the amendments to the claims overcome the rejection.

Claim 1 is amended herein to clarify that the mucosal cells are present in the mammal to which the recombinant gut colonizing microorganism is administered. In addition, Claim 1 has been amended to clarify that the protein is a **heterologous** protein (i.e. not native to the microorganism strain) under control of a promoter **consisting of** the nucleotide sequence of SEQ ID NO: 2, wherein the promoter is operatively interconnected to the nucleotide sequence encoding the heterologous protein, the recombinant gut-colonizing microorganism is a **bacterium**, the bacterium is administered **orally**, and the protein is expressed in mucosal cells **of the mammal**.

Support for the foregoing amendments can be found in the specification and claims as originally filed. In particular, applicants respectfully direct the Examiner to page 1,

lines 1-4, which disclose that the recombinant microorganisms are useful for delivery of antigenic material, and to page 5, lines 6-9, of the instant application wherein applicants disclose promoters P_{phoP}, and P_{pagC}, and P_{ompC}, which correspond to SEQ ID NOs: 2-4, respectively. Therefore, promoter P_{phoP} corresponds to **SEQ ID NO: 2**. Support for **oral** administration, can be found on page 8, lines 21-23 and page 16, lines 12-15 of the instant application. Support for expression of a **heterologous** protein can be found on, at least page 4, lines 24-36 of the instant application.

For at least the foregoing, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In the May 2, 2007 Office Action, the Examiner rejected Claims 1, 23 and 25-32 under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully submit that the amendments to the claims overcome the rejection.

As discussed above, Claim 1 has been amended to clarify that the method requires encoding a heterologous protein to be expressed under the control of a promoter **consisting of** a nucleotide sequence of SEQ ID NO: 2, the promoter being operatively interconnected to the nucleotide sequence in a recombinant gut-colonizing **bacterium**, and administering the bacterium **orally** to the mammal.

The Examiner cites the abstract of Titball *et al.* (WO 95/18231) for the proposition that certain constructs producing *Y. pestis* F1 antigen were found to be unstable. Applicants respectfully submit that although they may be working with the same antigen, Titball *et al.* fail to use a promoter consisting of the nucleotide sequence of SEQ ID NO: 2 as claimed in the present application. Page 10, lines 18-20, and Example 3 (see in particular page 16, lines 31-36) of the present application clearly describe the stability of the plasmids in the claimed method. Therefore, applicants have overcome the problems described by Titball *et al.* in other expression systems.

With regard to Claim 23, the Examiner quotes page 168 of the scientific paper of Leary *et al.* (*Microb. Pathogen.* 23:167-179, 1997) for the proposition that F1 antigen

alone does not confer protection against naturally occurring and genetically mutated F1-negative strains. Leary *et al.* teach that it is desirable to administer the F1 antigen with other antigens to provide effective protection against plague. Claim 23 is directed to a method of causing expression of a desired heterologous protein in mucosal cells wherein the heterologous protein induces a protective immune response against a pathogen. Applicants enclose a copy of the scientific paper of Oyston *et al.* (*Infect. and Immun.* 63:563-568, 1995), the abstract of which clearly discloses that F1 antigen alone is protective against plague by stating, "The immunity induced [from an *S. typhimurium* expressing F1 antigen] was able to protect mice against challenge with a virulent strain of plague."

Accordingly, applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Claim rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1, 23 and 25-32 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully submit that the amendments to the claims overcome the rejection.

Claim 1 has been amended to clarify that the method **causes** expression of the desired protein in mucosal cells of a mammal. Applicants submit that the preamble and body of the amended claim are now consistent.

With regard to the Examiner's question regarding whether the desired protein is expressed *in vivo* or not, applicants have amended Claim 1 to recite that the bacterium is **orally** administered to the mammal, thereby clarifying that the expression is *in vivo*.

In addition, applicants have amended Claim 1 as suggested by the Examiner to clarify that the heterologous protein is under **the** control of the promoter.

Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

The foregoing is submitted as a full and complete Response to the Non-Final Office Action mailed on May 2, 2007. For at least the reasons given above, applicants respectfully submit that the pending claims are described in the specification, enabled and definite. Accordingly, applicants submit that the claims in the present application are in condition for allowance, and such action is courteously solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application that may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

No additional fees are believed due; however the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account number 11-0855.

Respectfully submitted,

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